ABSTRACT OF RESULTS

a. Since Start of Project: This portion of the summary covers the period from 1 July 1951 to 31 December 1954. As stated above, the objective of the project is to find a synthetic drug which would be as effective and as safe from the points of view of human toxicity and addiction liability as is codeine. Although adequate synthetic substitutes for morphine are available, such a substance is needed because no such drug of the codeine-type is known. Seventy-five per cent of the needs for narcotics are for codeine rather than morphine. This means that the United States must continue to import and stockpile opium until an adequate synthetic substitute for codeine has been developed. The role of the NIMH Addiction Research Center in this investigation consists of the determination of the addictive properties of new drugs. The evaluation of the analgesic and antitussive effects must necessarily be made elsewhere.

The methods used for studying the addiction liabilities of new analgesics have been described in detail in the project descriptions and in previous progress reports. Drugs to be studied as synthetic substitutes for codeine are recommended as promising by the Committee on Drug Addiction and Narcotics of the National Research Council. When such drugs are received at the NIMH Addiction Research Center the human pharmacology of the compounds is studied by determining effects of various doses on blood pressure,

respiratory minute volume, body temperature, pupillary size, etc. Following completion of the basic pharmacological work, effects of the drugs on the behavior of former morphine addicts are evaluated by administering them in doses based on the results obtained in the pharmacological experiments. If the drug induces behavioral effects resembling those seen after administration of morphine or codeine, it is very likely to possess addiction liability. The ability of the drug to relieve or to prevent the appearance of symptoms of abstinence from morphine is next studied in patients strongly addicted to morphine. If the drug under test relieves or suppresses abstinence, it is judged to have addiction liability. In such experiments, the dose of the drug under test which is required to relieve or suppress the symptoms of abstinence and the degree of relief or suppression of abstinence are indices for comparison with the standard drug, codeine.

When an especially promising drug becomes available, it is studied by the direct addiction technic. This involves the administration of ascending doses to former addict volunteers over periods of time ranging between 30 to 180 days. During the addiction period, suitable measurements are carried out to detect and evaluate the development of tolerance. Finally, drugs are withdrawn abruptly, and observations for the development of abstinence symptoms made.

The drugs studied during the period 1 July 1951 to 31 December 1954 are tabulated below:

DRUG	ADDICTION LIABILITY (Relative to Codeine)	TOXICITY (Relative to Codeine)	POSSIBLE UTILITY
Levorphan (l-Dromoran)	Much higher	Greater	None
3-Methyl ether of Levorphan	Higher	Greater	If needed, could be used for mild pain
3-Methylmethylamino-1:1 (2' Thienyl) But-1-ene	Higher	Higher	None
3-Methylamino-1:1 (2' Thienyl) But-1-ene	Higher	Greater	None
Dextrophan (d-Dromoran)	Lower	Lower	None
Dextromethorphan (3-Methyl ether of Dextrophan)	Lower	Lower	Very promising for cough.
dl 2:2-Diphenyl-4 dimethyl-aminoethyl Valerate	Higher	Somewhat less	Slight possibilities for pain relief
d 2:2-Diphenyl-4 dimethyl-aminoethyl Valerate	Higher	About equal	Slight possibilities for pain relief
l 2:2-Diphenyl-4 dimethyl-aminoethyl Valerate	Higher	Somewhat less	Slight possibilities for pain relief
dl ethyl 2:2-Diphenyl-4-dimethylamino butyrate	Higher	Somewhat less	Slight possibilities for pain relief

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	DRUG	ADDICTION LIABILITY (Relative to Codeine)	TOXICITY (Relative to Codeine)	POSSIBLE UTILITY
1.	Alpha-l-Methadol	Higher	Higher	None
2.	Beta-dl-Methadol*	Higher	Lower	Unknown
3.	d-2, N-Dimethyl-3-hydroxy-Morphinan*	Higher	Less	Unknown
4.	l-2, N-Dimethyl-3-hydroxy-Morphinan*	Higher	Somewhat higher	Possible for relief of pain
5.	Mixtures (1-10, 1-5, 1-3) of Halorphine and Morphine*	Higher	About equal	Very limited possibilities
6.	4-4-Diphenyl-dimethylamino-Hexanone-3*	Higher	Somewhat higher	Very definite possibilities for cough and pain relief

Work not entirely completed during period 1-1-53 to 1-1-54

See below for further details.

b. Results During Current Reporting Period: The addictive properties of eight drugs (or classes of drugs) were evaluated wholly or in part during the current reporting period. Results are shown below under the individual headings.

1. l and d 2-N-Dimethyl-3-Hydroxy-Morphinan. Investigation of these two compounds was partially completed during the preceding reporting period (See Numbers 13 and 14 in Table above). The results previously obtained were confirmed. The dextro form of the compound was completely inert, devoid of addiction liability, and probably devoid of any important therapeutic properties. For this latter reason, it is not promising as a synthetic substitute for codeine. The levorotatory form of the drug, on the other hand, partially suppressed abstinence in patients who were strongly addicted to morphine. Sixty milligrams of the levo isomer every four hours were sufficient for this purpose. The levo isomer, therefore, has higher addiction liability than that of codeine, but less than that of morphine. Although this drug is not too promising, it might be of value in the event a safer agent is not developed.

2. 4-4-Diphenyl-6-dimethylamino-hexanone-3 (See No. 16 in Table above). In doses of 60 to 75 mg. every four hours, this compound suppressed almost completely symptoms out of abstinence from morphine in 5 patients who were strongly addicted to that drug. Its addiction liability, therefore, is judged to exceed that of codeine, but is somewhat less than

that of morphine. This compound represents another possible substitute for codeine since it is in active use in Germany as a cough suppressant. Furthermore, it should be a mild analgesic and is easily synthesized.

3. Benzylmorphine Myristyl Ester. This drug, which was developed in France, is insoluble in water and can be injected only as an oily oral suspension. For this reason, all work carried out with the drug has been by the oral route. Doses ranging up to 600 mg. orally did not induce any definite morphine-like effects in nontolerant addicts. Transient skin eruptions consisting of blotchy erythema and urticarial wheals were observed in both of the patients who received the largest doses. The drug was completely ineffective in suppressing abstinence from morphine. The drug is not regarded as a promising substitute since it is not a true synthetic, has too high toxicity, and is probably therapeutically inert.

4. Beta-dl-Methadol. In doses ranging between 30 to 100 mg. orally or subcutaneously, beta-dl-methadol did not induce evidence of morphine-like action in 10 nontolerant addicts. It was totally ineffective in suppressing symptoms of abstinence from morphine in strongly addicted patients. It is, therefore, judged to have no addiction liability. Since there is no clinical data available on the possible value of beta-dl-methadol as an antitussive or analgesic agent, its possibilities as a synthetic substitute for codeine cannot be evaluated at

the present time. This drug is, however, easily chemically convertible to [redacted]-dl-acetylmethadol, a drug with very high addiction liability. For this reason, it is unlikely that it would be regarded as being a safe substitute for codeine.

5. Addiction liability of Nalorphine-Morphine (1-10) Mixture. In previous reports it was shown that mixtures of Nalorphine and morphine were not likely to be abused by drug addicts since morphine-induced euphoria is effectively blocked for 3 hours by the Nalorphine and since injection of such a mixture would precipitate abstinence in addicted individuals. Previous direct addiction experiments with this mixture involved administration of very high doses ("addicting dose schedule"). No information was available on administration of "therapeutic doses" chronically. For this reason, 6 patients were given 10 mg. morphine plus 1 mg. Nalorphine every four hours for 30 days, after which the drug was withdrawn. The unpleasant side effects noted with "addicting" schedules did not appear with this "therapeutic" dose schedule. Definite, mild abstinence, however, appeared following withdrawal of the mixture, which was just as intense as symptoms of abstinence following withdrawal of morphine after administration of 10 mg. every four hours for 30 days to the same 6 patients. Therefore, in one sense, the addiction liability of the mixture is as great as that of morphine. For this reason, and because the Nalorphine-morphine mixture is rather ineffective orally, it

is not regarded as a promising substitute for codeine. Furthermore, it is not a true synthetic.

6. Morphine Antagonists Other than Nalorphine. Work is being undertaken in the hope of developing a morphine antagonist which is orally effective. The combination of such an antagonist with a synthetic such as methadone, or Racemorphan, might decrease addiction liability and, therefore, be regarded as a possible substitute for codeine. Work with four synthetic antagonists has been partly completed.

(a) Levallorphan. This is the levorotatory Morphinan analogue of Nalorphine. The drug has been shown to be an effective antagonist to morphine and Racemorphan, both subcutaneously and orally. The antagonistic effects persist longer than do those of Nalorphine. Serious toxic reactions may occur with subcutaneous doses greater than 5 mg. These toxic effects consist of nausea, vomiting and precipitous drops in blood pressure. Toxic effects of the compound in doses which might be used in mixtures are not of any serious consequence. Since the drug is effective orally it offers definite possibilities for the development of a mixture of the kind desired.

(b) Dextronalorphan. This drug is the dextrorotatory isomer of Levallorphan. As expected, it is quite inert and, therefore, is not a promising constituent of an antagonist-analgesic mixture.

(c) Levallomethorphan. This compound is the 3-methyl ether of Levallorphan and was found to be effective, either orally or subcutaneously, in antagonizing the effects of morphine or Racemorphan. Untoward side effects appeared with doses greater than 5 mg. While a definite possibility as a constituent of an antagonist-analgesic mixture, it possesses no advantages over the parent compound, Levallorphan.

(d) 3-Hydroxy-N-Propargyl-Morphinan. This compound is of especial interest since it produces analgesic effects in mice which are equal to those induced by meperidine. Despite this, the drug is an effective antagonist when administered subcutaneously, but is far less effective when administered orally. It has been shown to precipitate symptoms of abstinence from morphine in addicted patients and, therefore, it is not likely to be abused by such patients. It offers some promise as being a possible substitute for codeine for the relief of mild pain.

(e) l-3-Acetoxy-N-allylnormorphinan. This compound is also an effective antagonist when injected subcutaneously. It is far less effective orally and, therefore, is not as promising a constituent for an antagonist-analgesic mixture as is Levallorphan.

7. Narcotine. This compound, though not chemically related to morphine, is derived from opium, and in the past was regarded as a troublesome waste product of opium processing. Evidence has now become available that the drug is an effective

antitussive in [redacted] man and animals. If this is confirmed, the drug might be a possible substitute for codeine as an antitussive and would, therefore, have the effect of extending the supply of codeine derived from opium. In doses ranging up to 100 mg., either orally or subcutaneously, the compound does not induce morphine-like effects in nontolerant former morphine addicts. No untoward toxic effects were observed. It appears to be totally devoid of any ability to suppress symptoms of abstinence from morphine. This compound is, therefore, regarded as being very promising.

8. Dihydrohydrohydroxymorphine. This compound is the morphine analogue of eukodal (dihydrohydroxycodeinone). In doses of 2 to 3 mg. subcutaneously, it induces marked morphine-like effects, including euphoria. It relieves and suppresses abstinence from morphine completely. Its addiction liability and toxicity are far greater than those of codeinone. The drug is, therefore, not a suitable codeine substitute.

9. Propoxyphenone (4-dimethylamino-1, 2, diphenyl-2-propionoxy-3-methylbutane). This compound was recently submitted by the Committee on Drug Addiction and Narcotics. The animal pharmacology and preliminary clinical experiments indicate that this drug may have analgesic properties approximately equivalent to those of codeine. It is, therefore, a very important drug since to date the potential substitutes

for codeine have been antitussives rather than analgesics. So far, only preliminary toxicological information is available. In doses ranging up to 250 mg. orally no evidence of morphine-like effects or morphine-like euphoria have been observed in nontolerant former morphine addicts. No serious toxic effects have been observed.

SUMMARY. Of the compounds studied so far, two are regarded as extremely promising as antitussive agents. These compounds are Dextromethorphan and Narcotine. Clinical evaluation of the antitussive properties of both are currently underway and it seems probable that both compounds will soon come into the market as constituents of antitussive mixtures. These drugs, however, constitute an answer to only half the problem. In addition to its use as an antitussive agent, codeine is extensively used for the relief of milder grades of pain. As yet no drug is available which is known to be as effective as codeine for this purpose and which has as low addiction liability and as low toxicity.

PLANS FOR FUTURE:

Immediate Plans: During the coming six months we hope to partly complete studies of five compounds which have been submitted by the Committee on Drug Addiction and Narcotics. These compounds are Propoxyphenone (See par. 9 above), three members of the Azacycloheptane series, and Piperydimethadone.

The Azacycloheptanes are of great interest since no evidence of addiction liability to one of these compounds was detected in an experiment using monkeys at the University of Michigan. Preliminary clinical information has already indicated that these drugs may be effective analgesics. If this is true, and if their addiction liability is low, as indicated by the experiments at Michigan, they might be effectively substituted for codeine in relieving pain. The drug Piperydimethadone is also already in clinical use in Great Britain and, therefore, is of some interest. We also hope to proceed further with the development of antagonist-analgesic mixtures, with chief emphasis on Levallorphan. Further studies of 3-Hydroxy-N-Propargyl-Morphinan (direct addiction) are also indicated.

Long-range Plans: We intend to continue the search for an adequate synthetic substitute for codeine until a drug, or drugs, is found which are judged by the Committee on Drug Addiction and Narcotics of the National Research Council fulfill all the necessary requirements. Only suspension of the project due to lack of funds would cause work to cease prior to the attainment of this goal.

REPORTS AND PUBLICATION: (During current report period)

1. Isbell, H., and Fraser, H.F.: Addictive Properties of Methadone Derivatives (abstract). Federation Proc., 13: (1) 369 (Mar.) 1954.

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REPORTS AND PUBLICATIONS: (Cont'd)

2. Fraser, H.F., Nash, T.L., Van Horn, G.D., and Isbell, H.: Use of Miotic Effects in Evaluating Analgesic Drugs in Man. Arch. Internat. de pharmacodyn. et de therap., 93: (4) 443-45 (Aug.) 1954.

3. Reports to Committee on Drug Addiction and Narcotics, National Research Council:

   (a) Work of NIMH Addiction Research Center, Annual Report, 22-23 January 1954. Contains report on the addiction liabilities of Nalline-morphine mixtures; l and d 2-N-Dimethyl-3-Hydroxymorphinan; dl, l and d 2:2-Diphenyl-4-Dimethylaminoethyl valerates; dl Ethyl 2,2-Diphenyl-4-Dimethylamino-butyrate; 4-4-Diphenyl-6-Dimethylamino-Hexanone-3; dl 1-Methyl-4-Carbethoxy-Azacycloheptane; N-Propargyl-Dihydro-normorphine; l and d N-allylnormorphine; and N-Allyldiacetylnormorphine.

   (b) Addiction Liability of Narcotine, 2 October 1954.

   (c) Addiction Liability of Numorphan (Dihydrohydroxy-Morphinone), 2 October 1954.

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Director of Research

Attachments.

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